IJMEAR | International Journal of Medical Education And Research
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ORIGINAL RESEARCH ARTICLE
Vol. 5 · No. 3 · May 2026

Role of Reactive Oxygen Species in Cardiovascular Diseases:

A Comprehensive Literature Review

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ABSTRACT

Background: The reactive oxygen species (ROS) are highly reactive chemical substances produced during the process of oxygen metabolism that serve as an important factor in the causation of cardiovascular diseases (CVDs). Although physiological levels of ROS are required for cellular functions, excess production of ROS results in oxidative stress, endothelial dysfunction, and inflammation.. **Objective:** The objective of this review is to critically examine the available scientific literature regarding the role played by ROS in the development of various cardiovascular diseases such as atherosclerosis, hypertension, myocardial infarction, and ischemia-reperfusion injuries. **Methods:** This literature review seeks to systematically examine scientific data about the processes by which ROS participate in cardiovascular diseases such as atherosclerosis, hypertension, heart failure, and ischemia/reperfusion injury. Additionally, it will evaluate existing and upcoming therapeutic approaches based on antioxidants.**Results:** The main sources of oxidative stress in cardiovascular disease arise from ROS generated by NADPH oxidases, mitochondria, xanthine oxidase, and uncoupled endothelial nitric oxide synthase (eNOS). The mechanisms that contribute include oxLDL-induced foam cells in atherogenesis, superoxide-induced NO inactivation in hypertension, mitochondrial ROS-induced apoptosis in heart failure, and ROS produced by neutrophils during reperfusion injury. Therapeutic interventions that have demonstrated potential include antioxidants such as mitochondrial, NADPH oxidase, and gene therapy antioxidants. **Conclusion:** ROS occupy a central mechanistic position across diverse CVDs. Future research should prioritize source-specific ROS targeting and personalized antioxidant therapies to translate mechanistic insights into effective clinical interventions.

Keywords: *Reactive Oxygen Species; Cardiovascular Disease; Oxidative Stress; NADPH Oxidase; Antioxidant Therapy*

1. INTRODUCTION

1.1 Background

Cardiovascular diseases (CVDs) are the most common cause of morbidity and mortality across the globe, with an estimated mortality rate of 17.9 million people per year, according to the World Health Organization [1]. The multifactorial pathogenesis of CVDs encompasses a complicated balance between genetic, environmental, metabolic, and cellular factors. ROS are known to play critical roles in physiological and pathological processes and have been identified as significant mediators in the development of cardiovascular diseases [2]. ROS can be described as oxygen-containing substances such as superoxide anion (O2•−), hydrogen peroxide (H2O2), hydroxyl radical (•OH), and peroxynitrite (ONOO−), which differ in chemical structure and cellular targets [3]. At the physiological level, ROS are generated within strict limits as a result of cellular respiration and act as vital secondary signaling molecules involved in the control of vascular tone, cell proliferation, and immune response. Considering that the cardiovascular system experiences a high metabolic load due to the energy expenditure of the heart muscle, mechanical stress on vascular walls, and dependence on nitric oxide (NO) production for endothelial cells to maintain their function, the cardiovascular system is especially vulnerable to oxidative stress [4]. Oxidative stress arises when the generation of reactive oxygen species surpasses the ability of natural antioxidant systems such as SOD, catalase, glutathione peroxidase, and thioredoxin to handle them, leading to damage to the heart [5].

1.2 Problem Statement

Notwithstanding the notable progress in pharmacology and interventions for CVDs, the disease burden remains high on a worldwide scale, especially in developing nations [1]. However, one of the crucial problems that remain unresolved is the poor transfer of knowledge from mechanistic studies of oxidative stress to practical clinical application. In recent years, many randomized controlled clinical trials on antioxidant vitamins (C and E) showed no evidence of cardioprotective effects, thus posing serious questions about the intricacies of ROS metabolism in cardiovascular system physiology [6]. The dual functionality of ROS as both signal transmitters and destructive agents makes their targeting difficult. Furthermore, the multiplicity of enzymatic ROS generators, which include NADPH oxidases (Nox1, Nox2, Nox4), respiratory complexes in mitochondria, xanthine oxidase (XO), and uncoupled endothelial nitric oxide synthase (eNOS), makes an individual antioxidant strategy impossible [7]. It has been shown that the timing and location of the production of ROS are critical factors influencing whether an oxidant signal elicits a positive or negative response [8]. There are also differences

among patients with respect to genetic variants of antioxidant enzymes, coexisting diseases like diabetes and hypertension, and multiple drug therapies leading to variations in oxidative stress levels. Solving this problem requires a thorough examination of existing literature to determine knowledge gaps, conflicting results, and areas where further research should be focused [9].

1.3 Novelty and Significance

This literature review aims at adding to the existing literature by presenting an elaborate, mechanism-based review on the role of ROS in four major cardiovascular diseases: atherosclerosis, hypertension, heart failure, and I/R injury. While previous reviews on ROS in cardiovascular disease have either been too general or focused on one specific disease only, this review uses a cross-disease approach, which will help identify common and divergent molecular mechanisms, oxidative patterns specific to a given pathology, and differential susceptibility to different treatments [10]. In particular, this review pays attention to the relatively new concept of 'physiological' versus 'pathological' role of ROS in cardiovascular function. Moreover, this review critically evaluates current limitations in translating pre-clinical success in ROS manipulation into positive patient outcomes and highlights possible reasons for such a limitation due to overly reductionistic antioxidant approaches. Finally, the review discusses some promising new methods of modulating ROS levels, including mitochondria-targeted antioxidants, Nox inhibitors, and genetic approaches [11].

2. METHODS

2.1 Study Design

This research was performed by conducting a systematic review based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). No data were collected directly for this research; data were gathered from the literature only.

2.2 Literature Search Strategy

A comprehensive search of electronic databases was performed including PubMed/MEDLINE, Scopus, Web of Science, and EMBASE. The search was conducted between January 2024 and March 2025, covering publications from January 2000 to December 2024. The following Boolean search strings were employed:

> *PubMed: ("reactive oxygen species"[MeSH] OR "oxidative stress"[MeSH]) AND ("cardiovascular diseases"[MeSH] OR "atherosclerosis"[MeSH] OR "heart*

> *failure"[MeSH] OR "hypertension"[MeSH])*
> *Scopus: TITLE-ABS-KEY ("ROS" OR "superoxide" OR "hydrogen peroxide") AND ("cardiovascular" OR "endothelial dysfunction" OR "cardiac remodeling")*
> *MEDLINE: ("NADPH oxidase" OR "mitochondrial ROS" OR "xanthine oxidase") AND ("ischemia reperfusion" OR "vascular oxidative stress" OR "antioxidant therapy")*

2.3 Inclusion and Exclusion Criteria

Studies were selected for inclusion if: (1) they were published within peer-reviewed journals between 2000 and 2024; (2) they investigated the role of ROS in human cardiovascular disease and/or animal models of the same; (3) they were comprised of novel experiments or meta-analyses/reviews thereof; and (4) they were written in English. Exclusion criteria were set at: (1) being written as a conference proceeding, editorial, or letter to the editor lacking original findings; (2) only investigating non-cardiovascular disease models; or (3) not describing their methods of investigation for either ROS production or cardiovascular effects.

2.4 Data Extraction

Independent data extraction involved the following variables: type of research, principal ROS agent studied, cardiovascular disease, important findings related to ROS action, and implications for treatment. Disputes over data extraction were settled through consensus. Studies selected for inclusion were quality assessed using the Newcastle-Ottawa Scale for observational studies and Cochrane Risk of Bias tool for randomized clinical trials.

3. RESULTS

3.1 ROS Sources and Enzymatic Mechanisms in Cardiovascular Disease

Various enzymatic pathways are involved in the production of reactive oxygen species (ROS) in the cardiovascular system, with different regulatory controls and disease-related consequences. The NADPH oxidase (NOX) family enzymes represent the most important controlled source of ROS in the cardiovascular system. NOX2 is mainly localized in endothelial cells, phagocytic cells, and cardiomyocytes and is activated by cytokines, mechanical forces, and neurohumoral agents like angiotensin II (Ang II) to produce superoxide ion ($O_2^{\bullet-}$) [6]. Griendling et al. found that the activation of NOX2 and NOX4 in the presence of Ang II in vascular smooth muscle cells (VSMCs) leads to the continuous production of $O_2^{\bullet-}$ and results in VSMC hypertrophy and vascular remodeling [6]. In contrast, NOX4 continuously produces hydrogen peroxide (H_2O_2) that can act as a protective signaling molecule in some physiological

contexts [12].Mitochondria-derived ROS (mtROS) are produced via Complexes I and III in the electron transport chain, especially when there is metabolic dysfunction, ischemia, or calcium overload [7]. In heart failure, Tsutsui et al. found that mitochondrial ROS accumulation causes cardiomyocytes' apoptosis, affects their contractility, and triggers MMP activity leading to cardiac remodeling [7]. XO catalyzes the formation of superoxide and hydrogen peroxide as a consequence of purine metabolism, and the activity of this enzyme is dramatically increased in ischemia and heart failure. The use of an XO inhibitor such as allopurinol has shown some effects on improving endothelial dysfunction and preventing adverse cardiovascular outcomes in clinical studies [13]. An uncoupled state of the enzyme NOS results in superoxide production rather than nitric oxide due to a lack of BH4 or its substrate L-arginine. Förstermann and Münzel have provided substantial evidence for the pivotal role of eNOS uncoupling as a potent amplifier of vascular oxidative stress in hypertension and diabetes mellitus-induced vasculopathy [5].

3.2 ROS in Atherosclerosis and Endothelial Dysfunction

Atherosclerosis is primarily an inflammatory condition affecting the blood vessels where oxidative stress is causal and amplifying throughout the process of lesion formation. Initiation occurs via the oxidative modification of low-density lipoprotein (LDL) by reactive oxygen species (ROS) produced by vascular tissues through endothelial NADPH oxidases and lipoxygenases [9]. Oxidatively modified LDL (oxLDL) does not activate the normal LDL receptor and thus is endocytosed by macrophages using scavenger receptors (SR-A and CD36) causing foam cell formation—the hallmark of early atherosclerotic lesions [9]. In a study conducted by Madamanchi et al., oxLDL activation of NF-κB in macrophages causes increased production of cytokines such as IL-1β, TNF-α, and MCP-1, while in endothelial cells and VSMCs leads to increased production of VCAM-1 and ICAM-1—pro-inflammatory mediators and adhesion molecules responsible for vascular inflammation [9]. Endothelial dysfunction, characterized by impaired nitric oxide (NO) bioavailability, is one of the earliest events in oxidative stress-induced vascular pathology. Superoxide interacts diffusively with NO to produce peroxynitrite ($ONOO^-$), an oxidizing molecule, which nitrosylates proteins, oxidizes tetrahydrobiopterin (BH4) and causes DNA strand breakage [5]. In their study, Münzel et al. noted that patients suffering from cardiovascular risk factors had high levels of vascular superoxide and low flow-mediated dilation [10]. ROS also induce redox-sensing pathways such as protein kinase C (PKC), mitogen-activated protein kinases (MAPKs), and PI3K/Akt signaling pathway, leading to VSMC proliferation, senescence of endothelial cells, and ECM remodeling, all of which facilitate the development and progression of atheroma plaques [14]. Significantly, the mtDNA damage

observed in atherosclerotic lesion cells by Ballinger et al. indicates an iterative process of oxidative injury in which mtROS compromise mitochondria to produce additional ROS [14].

3.3 ROS in Hypertension and Heart Failure

These two diseases, hypertension and heart failure, are examples of CVDs where the pathological process can be initiated and maintained by ROS-dependent mechanisms. For instance, an impairment in endothelial-dependent vasodilation due to the inactivation of NO by superoxide is a critical pathological feature of hypertension. It has been established that the RAAS can activate vascular NADPH oxidases whereby the engagement of AT1 receptors by Ang II leads to the activation of Nox2 enzyme and generation of O2•− that not only decreases NO availability but also causes vasoconstriction, VSMC hypertrophy, and sodium retention in the kidney, leading to increased blood pressure [6]. Several experimental studies on Ang II-induced hypertension have reported elevated vascular superoxide levels, decreased SOD activity, and impaired endothelium-dependent vasorelaxation, all of which can be reversed via NADPH oxidase inhibition or antioxidant administration [15]. Excess mineralocorticoids, often seen together with hypertension, have also been found to increase ROS by increasing Nox expression through aldosterone [16].During the progression to heart failure, neurohormone overactivation and mechanical overload result in increased mitochondrial ROS generation. Excessive mitochondrial O2•− production by mitochondria within stressed cardiomyocytes is derived from Complex I and III and is associated with redox-dependent activation of calcineurin, CaMKII, and MAPK pathways, resulting in pathological hypertrophy, fibrosis, and loss of contractility [7]. Ago et al. and Sadoshima showed that the Trx1 system acts as an endogenous suppressor mechanism for ROS-induced hypertrophy; experimental overexpression of Trx1 suppressed pressure overload–induced cardiac remodeling [11]. In addition, Nakamura et al. and Sadoshima found that mtROS activates NF-κB and AP-1 transcription factors in cardiomyocytes, leading to the transcription of profibrotic cytokines such as TGF-β1 and CTGF, thus stimulating cardiomyocyte fibroblast and collagen deposition [12]. This will eventually stiffen the myocardium and hinder both diastolic and systolic function. Markers of systemic oxidative stress such as malondialdehyde, 8-isoprostane, and oxidized glutathione are significantly higher in patients with heart failure and are independent predictors of adverse outcomes [17].

3.4 ROS in Ischemia-Reperfusion Injury and Emerging Therapies

I/R injury is one of the best known examples of cardiovascular disorders associated with ROS involvement, because I/R injury results from a pathological increase in ROS production caused by the immediate post-ischemic re-establishment of blood flow [18]. Ischemia causes

ATP exhaustion followed by intracellular accumulation of calcium ions, mitochondrial membrane depolarization, and conversion of xanthine dehydrogenase into xanthine oxidase (XO) responsible for ROS production [13]. During reperfusion, due to the rapid reintroduction of molecular oxygen, XO and mitochondria electron transport chain generate an enormous number of superoxide ions and hydrogen peroxide [18]. In addition, neutrophils contribute substantially to the production of ROS through NADPH oxidase and myeloperoxidase activation leading to HOCl formation; as a result, there occurs ROS-induced peroxidation of cardiomyocytes' phospholipids, mPTP opening, and activation of apoptosis [19]. Opening of mPTP channel is critical in reperfusion injury, which is marked by mitochondrial swelling, release of cytochrome c and ultimately cell death, where ROS acts as trigger and consequence of the process [20]. Dhalla et al. showed that ROS and lipid peroxidation products, along with calcium dysregulation mediated by ROS, result in sarcoplasmic membrane damage and oxidation of cardiac contractile proteins leading to impaired heart functioning in ischemia/reperfusion injury [8]. Targeting ROS for treatment of I/R injury includes use of mitochondria targeted antioxidants, such as MitoQ and SkQ1, which are highly effective in scavenging mtROS compared to conventional antioxidants owing to their selective localization within mitochondria [21]. Though MitoQ has shown promising results in preclinical models in terms of infarct size reduction, its clinical application is still challenging. Another clinically effective approach is inhibition of cyclophilin D using CsA, which prevents mPTP channel opening in response to reperfusion [22]. Inhibitors of NADPH oxidase (GKT137831) that block Nox1 and Nox4 pathways have entered early stage clinical evaluation for vasculature and cardiac disease conditions. Gene therapies, such as administration of adeno-associated viral vectors to deliver over-expression of MnSOD (SOD2) and catalase, have been shown to confer significant cardioprotection in animals models of I/R damage [23]. Furthermore, pre-conditioning procedures involving remote ischemia induction have shown clinical benefit in cardiac surgeries through the beneficial effect of oxidative stress hormesis [24]. Thus, collectively, all these advancements illustrate the development of treatment strategies that utilize specific ROS regulation rather than general antioxidant administration.

Table 1. Summary of Included Studies on ROS Mechanisms in Cardiovascular Diseases

Study (Author, Year, Ref.)	Study Type	ROS Source/Focus	Key ROS Mechanism	Therapeutic Implication
Förstermann & Münzel (2006) [5]	Review	eNOS uncoupling	ROS from uncoupled eNOS impairs NO signaling, promoting hypertension	Antioxidant therapy may restore eNOS coupling
Griendling et al.	Experimental	NADPH oxidase	Ang II activates Nox2/Nox4;	NADPH oxidase as

Study (Author, Year, Ref.)	Study Type	ROS Source/Focus	Key ROS Mechanism	Therapeutic Implication
(2000) [6]		in VSMCs	increases O2•−	therapeutic target
Tsutsui et al. (2011) [7]	Clinical & Experimental	Mitochondrial ROS in HF	mtROS drives cardiomyocyte apoptosis and remodeling	MitoQ reduces cardiac dysfunction
Dhalla et al. (2000) [8]	Review	Oxidative stress & myocardial injury	Lipid peroxidation and Ca2+ overload in ischemic injury	Antioxidant pretreatment protective
Madamanchi et al. (2005) [9]	Review	ROS in atherosclerosis	Oxidized LDL activates NF-κB, macrophage foam cell formation	Statins reduce vascular oxidative burden
Münzel et al. (2010) [10]	Clinical Review	Endothelial dysfunction & ROS	Superoxide quenches NO; endothelial dysfunction precedes CVD	Vitamin C/E partially restore function
Ago & Sadoshima (2006) [11]	Experimental	Thioredoxin system & ROS	Thioredoxin-1 regulates ROS-mediated hypertrophy	Thioredoxin overexpression protects
Nakamura & Sadoshima (2018) [12]	Review	ROS and cardiac remodeling	ROS activates MAPKs, NFκB in cardiac fibrosis	Targeted antioxidant gene therapy
Dikalov & Harrison (2014) [13]	Review	Xanthine oxidase & vascular ROS	XO-derived ROS accelerates endothelial senescence	Allopurinol reduces cardiovascular events
Ballinger et al. (2002) [14]	Clinical	Mitochondrial DNA damage & CVD	mtDNA deletions correlate with atherosclerotic lesion severity	Mitochondria-targeted therapy promising

NADPH: Nicotinamide adenine dinucleotide phosphate; eNOS: Endothelial nitric oxide synthase; HF: Heart failure; CVD: Cardiovascular disease; VSMC: Vascular smooth muscle cell; ROS: Reactive oxygen species; Ang II: Angiotensin II; mtROS: Mitochondrial reactive oxygen species; XO: Xanthine oxidase; LDL: Low-density lipoprotein.

4. DISCUSSION

The results reviewed here highlight the significant and varied contribution of ROS in the onset, development, and perpetuation of cardiovascular disease. In the four main areas of pathophysiology covered by the study—atherosclerosis, endothelial dysfunction, heart failure/hypertension, and reperfusion injury—the presence of ROS is not only that of a secondary product but also that of an active player in the signaling process that communicates with almost all cardiovascular regulatory systems [2, 9]. This conceptual reframing of ROS from bystanders to orchestrators carries profound implications for therapeutic strategy.

The common thread found in the aforementioned literature review is the critical role played by ROS generated via NADPH oxidase in the pathogenesis of oxidative stress in the cardiovascular system. Specifically, the Nox enzymes, especially Nox2 and Nox4, have been identified as key regulators that act as the principal source of ROS in response to the presence of hemodynamic stress, neurohormonal stimulation, and inflammatory cues [6, 15]. The distinct biological properties of each enzyme (whereby Nox2 generates harmful O2•− and Nox4 produces potentially protective H2O2) complicate the use of pan Nox inhibitors and call for the

development of isoform-specific pharmacological agents [12]. This is the rationale behind the development of GKT137831.

The perceived ineffectiveness of non-selective antioxidants (such as vitamins C and E and beta-carotene) in extensive clinical trials (such as the Heart Protection Study and HOPE trial) can be explained by multiple reasons as elucidated by the mechanistic studies cited above [10]. To begin with, these compounds nonspecifically remove ROS without any discrimination between the harmful superoxide radicals and the necessary physiological role played by H2O2 in redox signaling, thereby interfering with beneficial redox signaling. Secondly, these antioxidants fail to concentrate at the subcellular sites where the pathogenic ROS are produced. Finally, their action might be inadequate to counteract the rapid enzymatic activity of ROS production from activated NADPH oxidases and defective mitochondria. The effectiveness of mitochondria-directed antioxidants like MitoQ in experimental animal models of I/R, with their ability to reach much higher concentrations within the mitochondria than in the plasma, reinforces this notion.[21]

The idea that ROS hormesis, whereby low ROS concentration is able to initiate signaling pathways such as those involving Nrf2 and HIF-1α activation of antioxidant genes, makes it even more challenging to develop therapies targeting ROS activity [24]. An example of how such ROS signaling can be utilized in order to protect against injury is remote ischemic preconditioning, wherein ROS is utilized rather than being removed entirely.

ROS systems are interlinked in ways that lead to self-reinforcing cycles of oxidative activity, making it very difficult to disrupt these processes. For instance, BH4 oxidation induced by superoxides leads to eNOS uncoupling, producing more superoxides, which inhibit NO, reduce antioxidant enzyme activity, and contribute to mitochondrial impairment – each of these factors reinforcing the preceding ones [5, 7]. Such a feedback cycle of oxidative activity implies that treatment would be most effective when targeting this cycle at its earliest stages. Indeed, there is evidence from clinical practice suggesting that antioxidant treatments work best in cases of primary prevention or elevated baseline oxidative stress levels.

The contribution of mitochondrial DNA damage not only as a result but also as a causative factor of oxidative stress in the context of cardiovascular diseases, demonstrated by Ballinger et al. using atheromatous tissue samples, provides a promising direction for biomarker development [14]. mtDNA fragments in the bloodstream may function as biomarkers of cardiovascular oxidative damage, facilitating a better patient stratification in terms of their suitability to receive antioxidant treatment. Also, there are known polymorphisms in genes

coding antioxidants (e.g., SOD2 Val16Ala and GPx1 Pro198Leu) that determine different susceptibility to CVDs and oxidative stress and might be used to customize treatment in accordance with pharmacogenomics principles [25]. The next clinical trials in this area will require biomarker stratification, pharmacological targeting of specific isoforms of antioxidant enzymes, and pharmacogenomics analysis.

5. CONCLUSION

In this extensive literature review, the mechanism of involvement of reactive oxygen species in the etiology of some cardiovascular disease states such as atherosclerosis, hypertension, heart failure, and ischemia/reperfusion injury have been systematically elucidated. The body of scientific literature provided in this review demonstrates that there is strong and robust experimental and clinical data supporting the concept that reactive oxygen species play key roles in cardiovascular pathology through various enzymatic sources such as NADPH oxidases, ETC, xanthine oxidase, and uncoupled eNOS.

A number of key points can be derived from this discussion. First, the effects of ROS on biological systems in terms of cardiovascular tissues are highly context-dependent, with ROS able to exert adaptive actions at physiological levels while exerting structural damage under pathological oxidative stress states. Such complex effects on the biological system imply that the therapeutic paradigm adopted in the treatment of cardiovascular diseases associated with high ROS production should be aimed at correcting rather than eliminating ROS signaling pathways. Second, the varied enzymatic origins of ROS associated with cardiovascular system, which exhibit different activating factors as well as act in diverse cellular compartments, imply that the targeted elimination of ROS should be achieved using selective rather than general strategies.

Third, the self-perpetuating role of oxidative stress in CVD, whereby ROS damage antioxidant enzymes, impair mitochondrial function, cause uncoupling of eNOS, and activate pro-oxidant transcription factors, emphasizes the need for early treatment prior to the reinforcement of these positive feedback loops. The implications of this are critical for preventing CVD and imply that an antioxidant therapy targeted at patients exhibiting elevated levels of oxidative stress based on their biomarkers will be more effective than supplementing the general population. Fourth, the idea of utilizing ROS hormesis for the purpose of remote ischemic preconditioning demonstrates that ROS are not only damaging agents but also endogenous cues.

The future research agenda in this field should encompass: (1) the creation and clinical testing of specific antioxidants for each ROS source and target cell compartments; (2) incorporating biomarkers of oxidative stress (8-isoprostanes, mitochondrial DNA degradation products, oxidized glutathione proportion) into cardiovascular risk stratification schemes and drug trials; (3) pharmacogenomics research focused on identifying the target groups of patients who will most benefit from antioxidant treatment; (4) elucidation of the impact of currently available cardiovascular drugs (statins, angiotensin-converting enzyme inhibitors, beta-adrenergic blockers) on ROS production as an element of their cardioprotective effect; and (5) examining the possibility of dietary and behavioral methods for improving the redox status in the cardiovascular system.

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